GENE THERAPY ADVISORY COMMITTEE

FIFTH ANNUAL REPORT

January 1998 – December 1998

Health Departments of the United Kingdom
1999

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CONTENTS

SECTION 1 – PROTOCOLS CONSIDERED BY GTAC (1998)

1.1 GTAC met four times during 1998 and assessed a total of 6 new protocols in committee. The Committee was satisfied for 4 of these research projects to proceed. One protocol was withdrawn by the proposers and one protocol was still awaiting final approval at the end of 1998.

1.2 In addition, the Committee received a number of requests from investigators to make amendments to existing approved gene therapy protocols. Whenever appropriate these were dealt with either by agreement with the Chairman or by postal circulation to Committee members. These are recorded in Section 2.

COLORECTAL CANCER

1.3 Colorectal cancer is the second commonest cause of cancer death in the U.K. It accounts for 28,000 new cases and 19,000 deaths annually.

1.4 Surgery can provide a treatment for colorectal cancer, but in order to be effective, it must be performed before the tumour has spread. At present the most widely used drug treatment for colorectal cancer is a combination of the drug, 5-fluorouracil (5-FU) with a type of vitamin B called folinic acid. This chemotherapy can induce tumour responses in 20-25% of patients, but may be associated with a range of unpleasant side effects. The outlook for patients with tumours that do not respond to these treatments is poor.

A pilot study of recombinant CEA vaccinia virus vaccine with post vaccination CEA peptide challenge in combination with 5-fluorouracil and folinic acid in the treatment of colorectal cancer. (GTAC 023)

1.5 Cancer cells have on their surface proteins that are not usually found on the surface of normal cells. These surface markers (tumour antigens) could potentially provide a way for the patient's immune system to recognise and selectively destroy the cancer cells. This study aims to enhance the ability of the immune system to recognise one such surface protein (carcinoembryonic antigen).

1.6 Carcinoembryonic antigen (CEA) is a 180kD glycoprotein found on the surface of the colorectal cancer cells. CEA is thought to have a role in cellular adhesion, cell to cell interactions, and possibly in glandular differentiation. The investigators propose to immunise patients with a gene therapy vector derived from vaccinia virus, which has been engineered to produce CEA.

1.7 Vaccinia virus is a member of the family of DNA containing viruses which also includes variola (smallpox virus), cowpox and monkeypox. It was the standard vaccine against smallpox. Since vaccinia usually elicits a strong immune response, it is hoped that because it also produces the CEA, immunity to the tumour antigen will be enhanced and that it will result in tumour rejection.

1.8 In this phase I study at Queen Elizabeth Hospital, Birmingham, patients will receive the CEA-vaccinia virus as an injection just below the surface of the skin on the first day of chemotherapy. Subsequent "booster" vaccinations will be given at four-weekly intervals. The patients will also receive standard chemotherapy whilst enrolled in the study.

1.9 The objectives of the trial are to determine the tolerance and side effects of vaccination with CEA-vaccinia virus in patients receiving chemotherapy for advanced colorectal cancer, to assess any evidence of anti-tumour activity in patients receiving the treatment, and to assess any evidence of an immune response to CEA.

1.10 GTAC considered the protocol at its February 1998 meeting and approval was granted on 2 March 1998. Delays have been encountered in the manufacturing process for the booster vaccine. The proposers have therefore suspended the trial until the manufacturers are able to supply the material.

OVARIAN CANCER.

1.11 Ovarian cancer is relatively common with 5,000 new cases annually in the UK and an annual death toll of 4,000. When the disease is recognised in the early stages, it is curable by

surgery. However, the majority of patients only seek medical help after the disease has already spread beyond the pelvis. In these circumstances surgery can only reduce the size of the original tumour. Small tumours which develop on the inside of the abdomen (on the peritoneal surface) are not amenable to surgical removal and are generally treated with chemotherapy (using the platinum compounds, cisplatin and carboplatin). The mean survival rate of women with late stage ovarian cancer is five years.

1.12 There is considerable interest in delivering chemotherapy for ovarian cancer directly to the peritoneal cavity, in order to increase the concentration of the drug at the site of the tumours and thus increase its effectiveness.

A phase I study of intraperitoneal administration of a replication deficient adenovirus carrying a nitroreductase gene in ovarian cancer patients. (GTAC 024)

1.13 A class of drugs, called "pro-drugs", which are used to kill cancer cells, are administered in an inactive form and are converted into an activated form in the patient's body. CB 1954 is a pro-drug that can be converted to a form, which is toxic to cells by the action of an enyzme called nitroreductase (with a corresponding 100,000 fold increase in cytotoxicity). CB 1954 is not an effective anti-cancer agent in man because humans do not make this enzyme.

1.14 The investigators propose to introduce a viral vector which carries the gene for a bacterial nitroreductase into the patient's tumour cells. The patient will then receive the pro-drug. Because the patient's tumour cells are producing nitroreductase, the CB 1954 will be activated within the tumour leading to death of the cancerous cells.

1.15 This approach is known as "virus directed enzyme prodrug therapy" (VDEPT) and is designed to increase the local concentration of anti-tumour drug beyond that which is possible with conventional administration. Nitroreductase activates the agent CB1954 to produce a potent toxic agent within the cancer cells.

1.16 The virus which will carry the nitroreductase gene into the tumour cells is a modified adenovirus. Adenoviruses cause infections of the respiratory tract but the virus used in this study will be altered so that it will be unable to cause such infections.

1.17 In this trial, in which the prodrug will not be administered, the primary objective is to determine how well patients tolerate intraperitoneal administration of the vector, and to assess its safety.

1.18 Patients whose ovarian cancer has relapsed and for whom no conventional drug treatment exists will be recruited into the trial at The City Hospital NHS Trust and The University Hospital NHS Trust, Birmingham.

1.19 GTAC reviewed this protocol at its February 1998 meeting and approval was granted on 2 March 1998. The adenoviral vectors are being manufactured with a view to beginning the trial in Spring 2000.

HEAD AND NECK CANCER

1.20 Head and neck cancer is the sixth most frequently occurring cancer in the world, resulting in an estimated 1,700 deaths in the UK during 1997.

1.21 The use of tobacco and consumption of alcohol are the two most important risk factors associated with this cancer. Surgery, radiotherapy, and (in more advanced cases) chemotherapy are standard treatments for head and neck cancer. Despite improvements in treatments, the overall 5-year survival rate for head and neck tumours remains amongst the worst of the major cancers.

A multiple ascending dose study evaluating the safety and gene transduction into malignant cells after administration of E1A-lipid complex by intratumoral injection with unresectable or metastatic head and neck tumours. (GTAC 025)

1.22 The E1A gene is derived from an adenovirus, a common type of DNA virus, which is primarily found in the respiratory tract. The product of the E1A gene has been shown to interact with

certain proteins produced by some cancer cells in a manner that affects the growth of the tumour.

1.23 Lipid molecules combine naturally with DNA to form a complex that has an affinity for cell membranes, which assists entry of the DNA into the cell. The investigators proposed to complex the E1A gene with a lipid carrier and to inject this complex into head and neck tumours. The toxicity and tolerance to the complex when injected into tumours would be determined and tumour response will be evaluated.

1.24 GTAC reviewed this protocol at its June 1998 meeting. Approval was declined on scientific and ethical grounds. The proposers were invited to submit a revised protocol. Following receipt by GTAC of a revised protocol, the proposers notified GTAC that they did not wish to pursue the submission.

MALIGNANT MELANOMA

1.25 Primary cutaneous malignant melanoma (skin cancer) has been increasing in prevalence over the past two decades. At present in the UK there are around 10 new cases per 100,000 of the population per year. This prevalence has doubled over a 15-year period. Mortality associated with melanoma is also rising although less rapidly. At present the overall 5-year disease free survival is approximately 70%. Survival prospects can be related closely to the thickness of the primary tumour at the time of its removal.

1.26 At present there is no effective non-surgical therapy to improve survival prospects for patients with thick primary cutaneous malignant melanomas. If the tumour is not removed at an early stage, the cancer spreads.

A study of dose requirements, safety and local efficacy of intratumoural injection of the genetically modified non-virulent herpes simplex virus HSV ICP 34.5 negative mutant 1716 into accessible soft tissue nodules of secondary malignant melanoma. (GTAC 026).

1.27 *Herpes simplex* is the virus responsible for causing cold-sores. The mutant form of *Herpes simplex* virus, HSV 1716 has the ability to kill dividing cancer cells but is claimed to be incapable of replicating in normal cells. In this study HSV1716 will be injected into soft tissue nodules of melanoma (which can be felt on the surface of the skin) of patients whose disease has spread and is no longer amenable to surgery.

1.28 The patients recruited will have proven melanoma with disease that has spread to other organs.

1.29 Toxicity and side effects of the virus will be assessed. The tumour nodules will be removed after injection and examined for evidence of virus replication and tumour cell damage.

1.30 The investigators will also determine whether injecting HSV 1716 into tumours will stimulate the immune system to attack tumours elsewhere in the patient's body that have not been directly injected.

1.31 GTAC reviewed this protocol at its June 1998 meeting and gave their approval subject to provision of further information on technical issues and a redrafting of the patient information leaflet. This proposal was approved by Chairman's action on 8 September 1998.

BREAST CANCER

1.32 Breast cancer is the most common cancer in women and the most common cause of death in women between the ages of 35 and 54 years. The 10-year survival rate in patients treated with surgery is about 70%, whereas, in patients whose disease has spread to the lymph nodes (and therefore cannot be completely surgically removed), the 10 year survival falls to 30%.

1.33 In the year 2000, it is predicted that between 1.1 and 1.4 million new cases will be diagnosed worldwide.

The use of MetXia-P450 for the treatment of advanced breast cancer. (GTAC 027).

1.34 The drug cyclophosphamide is a cornerstone in the conventional treatment of breast cancer patients. Cyclophosphamide can kill cells, but first it must be converted by an enzyme, cytochrome P450, to a form which is highly toxic for cells undergoing DNA replication, such as tumour cells.

1.35 The investigators have inserted the gene for human cytochrome P450 into a retroviral vector (designated MetXia P450). The vector will be injected into tumours which will direct the tumour cells to produce cytochrome P450, prior to the patient receiving cyclophosphamide. The tumour cells producing the enzyme should become much more sensitive to the drug than normal cells, thereby enhancing the drug's beneficial effects.

1.36 Patients with advanced breast cancer, who have cutaneous (and therefore accessible for injection) tumour nodules, will be recruited into this study at The Churchill Hospital, Oxford. This will be a phase I/II clinical trial of safety, gene transfer efficiency, gene expression, gene activity, immune response and dose regimen for the treatment of advanced breast cancer.

1.37 GTAC reviewed this protocol at its October 1998 meeting and gave their approval subject to receipt of an amended patient information leaflet.

SECTION 2 – AMMENDMENTS TO PREVIOUSLY APROVED PROTOCOLS/UPDATES

OVARIAN CANCER

A multiple ascending dose study evaluating the safety and the gene transduction into malignant cells after the administration of E1A-lipid complex by intra-peritoneal administration in patients with epithelial ovarian cancer who over-express HER-2/neu – A multi-centre trial (GTAC 022).

2.1 The original protocol was approved by GTAC in 1997. HER2/neu is a protein expressed by some types of cancer cells and is thought to contribute to the growth of tumours. The products of the E1A gene from adenovirus 5 (which causes respiratory tract infections) are known to inhibit HER2/neu expression in tumour cells. The investigators submitted two separate amendments to GTAC for approval.

2.2 **Amendment 1**. Approval was requested to continue treatment for a woman with advanced cancer who had completed the course of therapy permitted in the original protocol. The patient's tumour had regressed substantially and expression of the proto-oncogene HER-2/neu had fallen to levels found in normal cells. It was reported that the patient had remained free from side effects.

2.3 Following receipt of the patient's test results and an amended patient information leaflet, the amendment was agreed on 3 July 1998. The investigator did not continue the treatment of this patient.

2.4 **Amendment 2.** Patients with ovarian cancer often develop malignant ascites (a build-up of fluid in their abdomen containing cancer cells). The investigators reported that two patients receiving the E1A-lipid complex had experienced abdominal pain. The investigators sought approval to determine whether the presence or absence of ascites was related to this adverse effect of treatment.

2.5 Approval to recruit two groups of 3 patients (with and without ascites) was granted on 27 November 1998. These additional groups will bring the total number of patients in this study to 17 (the original protocol allows for up to 24 patients to be treated in total).

HEAD & NECK CANCER

A phase II trial of intravenous cisplatin, 5-FU and intratumoral injection with ONYX-015 into recurrent squamous cell tumours of the head and neck (GTAC 014B).

2.6 This protocol was initially discussed at the September 1997 meeting of GTAC and approved at the December 1997 meeting. The trial involves injecting tumours with a modified adenovirus designed to selectively reproduce in and kill cancer cells. Patients are also treated with chemotherapy using cisplatin and 5FU. The current amendment is in two parts: To extend the trial beyond the previous protocol limit if the patient seemed to have benefited from the treatment and to allow for a further blood test to be taken for the purpose of further investigation.

2.7 The amendments were approved by Chairman's Action on 8 September 1998.

UPDATES

2.8 Of the 32 gene therapy research protocols approved by GTAC or its predecessor, the Clothier Committee, since 1993, a total of 265 patients have been recruited (see Annex 6). Thirteen of these studies are now complete.

2.10 GTAC expects to receive detailed reports on current trials during 1999.

SECTION 3 – PROTOCOLS STILL UNDER CONSIDERATION AT THE END OF 1998

LIVER CANCER.

3.1 Colorectal cancer is the second commonest cause of cancer death in the UK. In more than 70% of all patients with recurrent colorectal cancer, despite current management regimes, the disease spreads to the liver.

3.2 For patients with metastatic liver tumours, chemotherapy provides only modest benefit, mainly in the form of pain relief or easing of other symptoms.

A phase I/II study of hepatic artery infusion with wtp53-CMV-AD in primary and metastatic malignant liver tumours. (GTAC 028)

3.3 The human p53 gene suppresses tumour growth and loss of the wild-type (normal) function of p53 is associated with the uncontrolled growth of many human cancers. By introducing a normal copy of the p53 gene into p53 deficient tumour cells it has been shown that tumour growth can be reduced and apoptosis (programmed cell death) promoted.

3.4 Adenoviruses cause infections of the respiratory tract. The vector wtp53-CMV-Ad is a replication-defective adenovirus (altered so that it cannot cause infections) which contains a gene for normal (wild-type) p53 (expression is under the control of the human cytomeglovirus immediate early promoter-enhancer).

3.5 In this phase I study at the Hammersmith Hospital the vector will be administered by infusion via the hepatic artery to patients who have incurable metastatic malignant tumours of the liver which are p53 deficient. The study seeks to determine the maximum safe dose of the vector and to determine its efficacy in the treatment of these tumours.

3.6 In October 1998 GTAC gave conditional approval subject to receiving a satisfactory response on a number of points, including amendments to the patient information leaflet and consent form.

SECTION 4 – GENERAL COMMENTS ON PROTOCOLS

4.1 All of the proposals submitted to GTAC during the fifth year have been aimed at developing treatments for cancer. There have been no new proposals targeting single gene disorders since 1996.

4.2 This year has seen the first application for approval to continue treatment for a patient who had completed the course of therapy permitted in the original protocol. Following receipt of the patient's test results which demonstrated that her tumour had regressed substantially, Chairman's Approval was granted for her continued treatment. It is hoped that this patient will be the first of many to demonstrate an apparent benefit from treatment with gene therapy.

4.4 All investigators are to be complimented on the way that they have responded to the requests for additional information. The Committee is grateful to proposers for their patience in answering the wide range of questions raised during the review process.

4.5 GTAC will continue to seek advice as appropriate from expert advisers. The Committee wishes to record its thanks to the expert assessors for their invaluable and constructive contribution to the work of GTAC and to welcome the contribution of those who have joined GTAC's panel of advisors during 1998.

4.6 Dates for GTAC meetings during 1999 are:

10 February

12 May

14 July

13 October

15 December

SECTION 5 – THE GTAC NEW & EMERGING TECHNOLOGIES SUBGROUP (NETS)

THE NETS SUBGROUP

5.1 At its September 1997 meeting GTAC agreed to establish a subgroup on New and Emerging Technologies (NETS). The remit of the subgroup is to aid GTAC to fulfil of its terms of reference "to advise UK Health Ministers on developments in gene therapy research and their implications". The subgroup's function is to report to GTAC on areas of any new technology that may have implications for gene therapy research or techniques.

The GTAC report on the potential use of gene therapy *in utero*

5.2 There are many inherited disorders in which the effect on the fetus begins in the womb. At present it is only possible to offer prenatal genetic tests to determine whether the developing fetus is affected and, within the legislative framework, to provide information to allow the parents to decide whether to proceed with the pregnancy. In the future, it may be possible that a successful intervention *in utero* could offer the alternative of the birth of a healthy child.

5.3 NETS was asked to look at the potential of gene therapy *in utero* and presented its initial report to GTAC in February 1998. The conclusions reached by NETS are primarily aimed at professionals and set out an ethical framework for *in utero* gene therapy.

5.4 The subgroup, adhering to the principles which govern consideration of conventional gene therapy, considered the key issues raised by gene therapy interventions *in utero*. NETS recommended that direct gene therapy *in utero* was unlikely to be acceptable for the foreseeable future due to ethical and safety issues.

5.5 However, certain conditions would be amenable to correction by the introduction of genetically modified stem cells. NETS concluded that *in utero* transplantation of genetically modified stem cells would be acceptable. GTAC would therefore consider applications for research involving the genetic modification of stem cells prior to transplantation in the same manner as somatic gene therapy.

International developments related to *in utero* gene therapy

5.6 The National Institutes of Health's Recombinant DNA Advisory Committee (RAC) initiated a debate on *in utero* gene therapy at is meeting on 24-25 September. The RAC discussed two "pre-protocols" for *in utero* therapies submitted by Professor W. French Anderson, a geneticist at the University of Southern California. Anderson, who led the team that performed the first gene therapy experiments on humans 8 years ago, submitted these proposals as a means of stimulating public debate. The advisory panel were asked to weigh the medical and ethical implications of the world's first proposed gene therapy in the womb.

5.7 The RAC will hold a gene therapy policy conference early in 1999 to discuss issues related to *in utero* gene therapy.

5.8 The UK is to date the first and only country to issue guidance in relation to the potential use of gene therapy *in utero*[2].

[2] Report on the Potential Use of Gene Therapy In Utero, Gene Therapy Advisory Committee, Health Departments of the United Kingdom, November 1998.

SECTION 6 – SECOND GTAC WORKSHOP

The Workshop

6.1 The first GTAC Workshop took place on 21 March 1997 and was entitled *Myth and Reality: Hope and Practicality.* One of the key issues identified at this workshop was the challenge of improving both efficacy and safety of gene therapy through improvements in therapeutic targeting. Accordingly, this issue was chosen as the topic for discussion at GTAC's second workshop, *"Hitting the Target with Gene Therapy"*, which was held on 19 November 1998, at the Department of Health, Elephant and Castle, London.

6.2 Seventy places were reserved on a "first come first served" basis and sixty-eight delegates gathered to participate on the day. The morning session comprised of four formal presentations and these were followed in the afternoon by "break-out" groups to discuss issues raised, a plenary session and open discussion.

The Speakers

6.3 The workshop was chaired by Professor Norman C Nevin, the current Chairman of the GTAC. The speakers were Professor Duncan Geddes (Brompton Hospital), Dr Steve Russell (Mayo Clinic, Rochester, USA), Dr Claudia Mickelson (Chairperson of the NIH Recombinant DNA Advisory Committee) and Professor Robin Gill (University of Kent at Canterbury).

The Discussion Groups

6.4 Following the formal presentations, delegates divided into three breakout groups, each charged with addressing issues related to non-target effects of gene therapy from their particular perspective and with the aim of reaching a consensus. The main conclusions reached by the breakout groups and plenary discussions were:

(i) Science & Technology Group

If targeting could be perfected then many of the safety mechanisms currently in place with regard to vector disablement would become redundant which in turn may increase efficacy of the treatment. Targeting could open the door to therapies that would involve injecting the gene therapy vector into the blood stream. These developments would represent major advances in efficacy, comfort and convenience for the patient.

(ii) Germline Group

A distinction was drawn between inadvertent germline alterations and germline gene therapy. No consensus was reached regarding the relative importance of the patient's health versus the possibility of trans-generational effects. The group agreed that it would never be possible to reduce the risk of germline effects to zero, but that an achievable and desirable goal would be to minimise these risks such that the possibility of germline contamination could be judged as "remote".

(iii) Ethics Group

Ethical discussion of gene therapy is concerned with risk and benefit. The Group considered the questions "can risk be quantified?" and " what level of risk is ethically acceptable?" However, it is argued that risk is by no means the only ethical issue in gene therapy. Other issues are the benefit out-weighing the risk, the justification for using invasive procedures and can benefit be achieved. A proper balance has to be struck between the ethically appropriate caution and ability to provide truly important benefit to the patient. With evolving technologies, particularly gene targeting, not only will the risks diminish but the benefits will increase for the patient.

Proceedings of the workshop.

6.5 The proceedings of the workshop, including the speakers' abstracts will be published on the Department of Health Homepage on:

http://www.open.gov.uk/doh/genetics/htm.

SECTION 7 – REFERENCES

[1] Gene Therapy Advisory Committee: First Annual Report January 1994-December 1994. Health Departments of the United Kingdom. London. Department of Health. March 1995.

[2] Gene Therapy Advisory Committee: Second Annual Report January 1995-December 1995. Health Departments of the United Kingdom. London. Department of Health. May 1996.

[3] Gene Therapy Advisory Committee: Third Annual Report January 1996-December 1996. Health Departments of the United Kingdom. London. Department of Health. June 1997.

[4] Gene Therapy Advisory Committee: Fourth Annual Report January 1997-December 1997. Health Departments of the United Kingdom. London. Department of Health. June 1998.

[5] Gene Therapy Advisory Committee: Report on the Potential Use of Gene Therapy *In Utero*. Health Departments of the United Kingdom. London. Department of Health. November 1998.

SECTION 8 – GLOSSARY

Adenovirus / adenoviral

A DNA virus, usually associated with mild upper respiratory tract infections.

Ascites

An abnormal accumulation of fluid in the abdominal cavity.

DNA (deoxyribonucleic acid)

The chemical (nucleic acid) substance in chromosomes and genes in which genetic information is coded.

Cell

The smallest unit of living organisms. It has been estimated that the body of a human adult comprises 50 million, million cells.

Cytotoxicity

The property of being able to directly kill cells.

Gene

Genes are the biological units of heredity – a sequence of DNA which codes for one *protein*. It has been estimated that the human genome comprises in excess of 100,000 genes.

Genetic Test

A DNA, chromosome or biochemical test, carried out on a sample of the patient's tissue (usually blood), that can be used for diagnostic or predictive purposes.

Gene Therapy

The genetic modification of *somatic cells*, by addition, insertion or replacement of a normal gene(s) to alleviate inherited or acquired diseases.

Genetic disease or disorders

Conditions which are due to defects in the genetic constitution of an individual. They may be the direct consequences of defects in single genes; or in whole chromosomes, parts of which may be lost, duplicated or misplaced; or due to the interaction of multiple genes.

Germline cells

Cells in embryonic life that become sperm in males and eggs in females and transmit genetic information to the next generation.

Herpes simplex

The virus responsible for causing cold-sores.

Immune response

A specific white blood cell or antibody response against an antigen (protein).

Immunomodulation

The use of a drug to alter, suppress or strengthen the body's immune system.

In Utero

In the womb (uterus).

Lipid

A fatty substance.

Malignant

Cells that have lost their normal control mechanisms and develop into a cancer.

Metastatic, metastases

Cancer which has spread from the site of the original tumour to other tissues/organs in the body.

Prodrug

Relatively inert compounds that can be converted to an active or toxic form.

Promoter

A short piece of DNA contiguous with a gene which controls whether or not (and at what rate) the corresponding *protein* is produced.

Protein

Proteins are essential constituents of the body that are coded for by DNA. They form the structural materials of muscles, tissues, organs, and are regulators of function, as enzymes/hormones.

Proto-oncogene

Genes which play a role in cell division. There is evidence to suggest that certain cancers are caused by activation (switching on) of these genes.

Retrovirus / retroviral vector

A type of virus used in gene therapy as a vector. Such viruses are usually animal viruses rather than agents of human disease. They are made inert so that they can enter a human cell carrying a gene for gene therapy without causing disease.

Somatic Cell

The cells which make up the body of an individual excluding the egg or sperm cells.

Stem Cells

A cell that can self renew and produce all the types of cells.

Tumour regression

A cancer that has become smaller or has completely disappeared.

Tumour suppressor genes

Such genes produce proteins to regulate the rate at which cells divide. The absence or dysfunction of a tumour suppressor gene is associated with the production of cancer cells.

Unresectable

Unable to be fully removed by surgery.

Vaccinia

A member of the family of DNA-containing viruses which also includes smallpox virus. It was the standard vaccine against smallpox.

Vectors

A carrier, usually a virus or lipid, to transport foreign DNA across the cell membrane into the cell.

Virus

A protein covered DNA or RNA containing organism which is only capable of reproducing within the host cell. Some viruses cause disease, such as chicken pox or influenza. Viruses suitably modified can be used as means of delivering a gene into cells.

ANNEX 1 – GTAC TERMS OF REFERENCE

The terms of reference of the Gene Therapy Advisory Committee (GTAC) are:

(1) To consider and advise on the acceptability of proposals for gene therapy research on human subjects, on ethical grounds, taking account of the scientific merits of the proposals and the potential benefits and risks;

(2) To work with other agencies which have responsibilities in this field including local research ethics committees and agencies which have statutory responsibilities - the Medicines Control Agency, the Health and Safety Executive, and the Department of the Environment;

(3) To provide advice to UK Health Ministers on developments in gene therapy research and their implications.

The Committee will have a responsibility for:

(a) Providing advice for applicants on:

(i) The content of proposals, including the details of protocols, for gene therapy research on human subjects;

(ii) The design and conduct of the research;

(iii) The facilities necessary for the proper conduct of the research;

(iv) The arrangements necessary for long term surveillance and follow up.

(b) Receiving proposals from doctors who wish to conduct gene therapy research on human subjects, and making an assessment of:

(i) The clinical status of the subjects;

(ii) The scientific quality of the proposal;

(iii) The scientific requirements and technical competence necessary for carrying out gene therapy research effectively and safely;

(iv) Whether the clinical course of the particular disorder is known sufficiently well for

(a) Sound information, counseling and advice to be given to the subject (or those acting on behalf of the subject);

(b) The outcomes of therapy to be assessable;

(v) The potential benefits and risks for the subject of what is proposed.

ANNEX 2 – MEMBERSHIP OF GTAC

Chairman

Professor Norman C Nevin BSc, MD, FFPHM, FRCPath, FRCPEd, FRCP
Department of Medical Genetics, The Queen's University of Belfast and
Belfast City Hospital

Members

Professor Elizabeth Anionwu, PhD, RGN, Dean of Nursing,
Wolfson School of Health Sciences
London

Mrs Rosemary Barnes
Chief Executive, Cystic Fibrosis Trust
Kent

Professor John Burn MD, FRCP
Northern Genetics Service
Royal Victoria Infirmary
Newcastle

Professor Anthony Dayan MD, FRCP, FRCPath, FFPM, FIBiol
St Bartholomew's & The Royal London School of Medicine & Dentistry
Department of Toxicology
London

Reverend Dr Keith Denison MA, PhD
The Church in Wales
Diocese of Monmouth

Dr Brenda Gibson FRCP, FRCPath, DFM
Department of Haematology
Hospital for Sick Children
Glasgow

Professor Ian Hart BVSC, MRCVS, PhD, FRCPath
United Medical & Dentistry Schools of Guy's and St Thomas' Hospitals
London

Mrs Ann Hunt
Tuberous Sclerosis Association

Professor Patrick Johnston
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Professor Theresa Marteau* MSc, PhD, CPsychol
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Guy's Campus, London

Professor James Neil BSc, PhD, FRSE
Department of Veterinary Pathology
University of Glasgow Veterinary School

Professor Anthony Pinching DPhil, FRCP
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St Bartholomew's and The Royal London School of Medicine & Dentistry
Queen Mary & Westfield College
London

Miss Eleanor Platt QC*
The Temple
London

Sir Brian Richards CBE, BSc, PhD*
Peptide Therapeutics Group
Cambridge

Professor C Michael Steel MB, ChB, PhD, DSc, FRCP Ed, MRCPath
School of Biological & Medical Sciences
University of St Andrews

Mrs Irene Train RGN, RM, RHV, QIDN
Formerly Director Public Health Nursing
Clwyd Health Authority

* **Members whose appointments came to an end on 31 December 1998.**

Observers

Dr Elaine Gadd
Department of Health
London

Dr Jenny Sims
Medicines Control Agency
London

Dr Brian Davis
Medicines Control Agency
London

Dr Lincoln Tsang
Medicines Control Agency
London

Secretariat

Mr Anthony J Taylor
Dr Jayne Spink
Mrs Margaret Straughan

ANNEX 3 – REGISTER OF MEMBERS INTERESTS

GTAC members have declared the following personal share holdings or funding from the biotechnology/pharmaceutical industry.

Professor Norman C Nevin	None
Professor Elizabeth Anionwu	None
Mrs Rosemary Barnes	Director, Association of Medical Research Charities Non-Executive Director, Greenwich Healthcare Trust Non-Executive Director, Greenwich Building Society (now Portman Building Society)
Professor John Burn	Clinical Advisory, Therexsys PLC
Professor Anthony Dayan	Consultancies: Cantab, Fournier, Introgene, Schering Plough & Therexsys PLC
Reverend Dr Keith Denison	None
Dr Brenda Gibson	None
Professor Ian Hart	None
Mrs Ann Hunt	None
Professor Patrick Johnston	Research grant from Bristol Myers Squibb Consultancy, Eli Lilly
Professor Theresa Marteau	None
Professor James Neil	Research grant from Intervet International BV Ad hoc consultancy, Q-One Biotech
Professor Anthony Pinching	Infrequent consultancies with Roche, Pharmacia Upjohn, Glaxo Wellcome. Travel Sponsorship from Boehringer Ingelheim and Glaxo Wellcome
Miss Eleanor Platt QC	Personal Shareholder in SmithKline Beecham, Glaxo Wellcome and Smith & Nephew Associated Companies
Sir Brian Richards CBE	Chairmanship, Oxford Biomedica Chair of Peptide Therapeutics Group PLC, Alizyme PLC, and CeNeS Limited Board member of Innogenetics BV, ICRT and Prelude Trust PLC
Professor C Michael Steel	None
Mrs Irene Train	None

ANNEX 4 – EXTERNAL EXPERT ADVISERS TO GTAC

During 1998 GTAC sought the views of the following expert advisers during the review of protocols submitted to the Committee.

Professor John Arrand
Paterson Institute for Cancer Research, Manchester.

Professor Kay Davies
Department of Human Anatomy & Genetics, University of Oxford.

Professor Don Jeffries
St Bartholomew's & Royal London School of Medicine and Dentistry.

Dr Nick Jones,
ICRF, Lincoln Inn Fields, London.

Dr Jonathon A Ledermann
University College London

Professor R Leonnard
Western General Hospital, Edinburgh.

Professor PR Lowenstein
University of Manchester.

Professor AC Minson
University of Cambridge.

Mr Graeme Poston
Royal Liverpool Hospital.

Professor MA Richards
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Dr Adrian Thrasher
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Professor Richard Vile
Mayo Clinic, Rochester, USA.

Professor D Wynford Thomas
University of Wales College of Medicine
Cardiff

Professor CR Wolf
University of Dundee.

Dr Maria Zambon
Central Public Health Laboratory
Collindale, London.

ANNEX 5 – NEW EMERGING TECHNOLOGIES SUBGROUP

Members of the GTAC New Emerging Technologies Subgroup are:

Reverend Dr Keith Denison (Chairman)
The Church in Wales
Diocese of Monmouth

Mrs Rosemary Barnes
Chief Executive
Cystic Fibrosis Trust
Kent

Dr Brenda Gibson
Department of Haematology
Hospital for Sick Children
Glasgow

Professor Ian Hart
UMDS
St Thomas' Hospital
London

Mrs Ann Hunt
Tuberous Sclerosis Association

Professor C Michael Steel
School of Biological & Medical Sciences
University of St Andrews

Mrs Irene Train
Formerly Director Public Health Nursing
Clwyd Health Authority

ANNEX 6 – GENE THERAPY RESEARCH 1993-1998

Protocol	Details	Centre	Outline Approval	Trial Commenced	Vector/ gene	Packaging cell line	No. of Patients
001 CLOSED	SCID-ADA	Institute of Child Health / Great Ormond Street Hospital	1-93	3-93	pLGAL	pOAM-P1	1
002 CLOSED	CF Nasal trial	Royal Brompton Hospital	3-93	9-93	Liposome DC-Chol/CFTR	-	15
003	B-cell lymphoma	MRC Cambridge	7-93	11-94	pVAC1/anti-idiotype immunoglobulin	-	7
004	Neuroblastoma	ICRF Bristol	2-94	Trial withdrawn	LNL-6/neo G1N-neo	PA317	-
005	Metastatic melanoma	ICRF Oxford	5-94	6-95	pNASSB-BGal pNASSB-IL2	-	13
006 CLOSED	Metastatic melanoma	Institute of Cancer Research /Royal Marsden Hospital	2-94	10-94	MFG-S-IL2	GP+env AM12	12
007 CLOSED	CF Nasal trial	Oxford/Cambridge	2-94	5-95	Liposome DC-Chol/CFTR	-	12
008 CLOSED	CF Nasal trial	Edinburgh	5-94	6-95	Liposome DOTAP-CFTR	-	16
009	CF lung trial	Royal Brompton Hospital	9-94	-	Liposome DC-Chol/CFTR	-	-
010 CLOSED	Lymphoma	University College London Medical School	12-94	10-95	pHaMDR-1	AMI2M1	3
011 CLOSED	Breast Cancer	Hammersmith Hospital	10-95	10-95	pERCY	-	12

Protocol	Details	Centre	Outline Approval	Trial Commenced	Vector/ gene	Packaging cell line	No. of Patients
012 CLOSED	Cervical Carcinoma	University of Wales, Cardiff	6-95	9-95	TA-HVP	-	1+8
012A	Cervical intraepithelial neoplasia III	University of Wales, Cardiff	5-96	9-96	TA-HVP	-	12
012B CLOSED	Cervical Cancer	University of Wales, Cardiff/University of Manchester	8-97	1-98	TA-HVP	-	8
013	Hurlers Syndrome	Royal Manchester Children's Hospital, Manchester	12-95	5-97	pLX	GP+env AM12	3
014 CLOSED	Head and Neck Cancer	Beatson Oncology Centre, Glasgow	1-96	3-96	Onyx-015	Human embryonic Kidney cell line 293	30
CLOSED	Head and Neck Cancer Phase II Study	Beatson Oncology Centre, Glasgow	7-97	7-97	Onyx-015	"	30
014A	Recurrent/Refractory ovarian cancer	Beatson Oncology Centre, Glasgow	2-97	3-97	Onyx-015	-	12
015	CF Nasal Trial	Oxford/Cambridge /Leeds/Manchester Consortium	5-96	7-96	Liposome DC-Chol/ CFTR	-	11
016 CLOSED	Head and Neck Cancer	Institute of Cancer Research Royal Marsden Hospital	9-96	12-96	SCH 58500	Human embryonic Kidney cell line 293	-
017 CLOSED	CF Lung and Nasal Trial	Royal Brompton Hospital	11-96	11-96	pCF1-CFTR # 67	-	16
018	Glioblastoma	Beatson Oncology Centre, Glasgow	12-96	10-97	HSVI ICP 34.5-1716	BHK 21/C13	9

Protocol	Details	Centre	Outline Approval	Trial Commenced	Vector/ gene	Packaging cell line	No. of Patients
019	Glioblastoma	Beatson Oncology Centre, Glasgow/Institute of Neurological Sciences, Glasgow	3-97	Trial withdrawn	SDZGLI328 HSV-TK	PA317	-
020	Gatrointestinal cancer/ /malignant cancer ascites	Royal Marsden Hospital, London	4-97		Ad5CMV-p53	293 cell line	1
021	Breast Cancer	Guy's Hospital, London	11-97		TG 1031	-	11
022	Ovarian Cancer	The John Radcliffe Hospital, Oxford Guy's and St Thomas's Cancer Centre, London Royal Marsden Hospital, London. St George's Medical School, London.	9-97	1-98	E1A Lipid complex	-	22
023	Colorectal Cancer	Queen Elizabeth Hospital Birmingham	3-98	-	Vaccinia virus	-	-
024	Ovarian Cancer	City Hospital NHS Trust andUniversity Hospital NHS Trust Birmingham	3-98				
025	Head and Neck	Royal London Hospital/ Charing Cross Hospital	-	Submission withdrawn	E1A-lipid	-	-
026	Malignant Melanoma	Western Infirmary Glasgow/ Southern General Hospital Glasgow	9-98		HSV1716		
027	Breast Cancer	The Churchill Oxford	10-98		MetXia p450		
028	Liver Cancer	Hammersmith Hospital, London	Under Consideration at end of 1998		WTp53Ad		

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